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Brief report

Changes in [^{3}H]-glutamate uptake into platelets from patients with bipolar I disorder

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Abstract

Glutamate is the most abundant excitatory neurotransmitter in the mammalian brain, and it is increasingly being implicated in the pathophysiology of mental illness. In fact, changes in glutamate neurotransmission seem to be involved in the etiology of schizophrenia, major depression and bipolar disorders. Furthermore, the alterations in platelet sensitivity in major depression are distinct from those of bipolar disorders. The aim of the present investigation was to determine whether patients with bipolar disorders exhibited differences in [^{3}H]-glutamate uptake of platelets. [^{3}H]-Glutamate uptake of platelets from controls ($n=14$), patients with bipolar disorders under lithium treatment (600–1800 mg/day for 6 months) ($n=7$) and patients with bipolar disorders with psychotic features ($n=8$) were carried out. Analysis of blood platelets from the three groups of subjects revealed significant differences in [^{3}H]-glutamate uptake between the control and psychotic patients. The specific glutamate uptake for the control and psychotic groups was 20.5 ± 8.4 and 37.5 ± 18.1 pmol glutamate/mg protein/10 min, respectively (mean $\pm$ SD). These results indicate that peripheral glutamate metabolism of platelets is modified in bipolar disorders and that more detailed studies must be carried out to determine whether these peripheral modifications correlate with central modifications in humans and in animal models of the disease.

Keywords: Glutamatergic neurotransmission; Platelets; Lithium treatment; Psychiatric disorders

1. Introduction

Glutamate is the main excitatory amino acid in the central nervous system of mammals and plays a fundamental role in a variety of neurophysiological/neuropsychological processes, including learning and memory formation (Lipton and Rosenberg,

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1994; Ozawa et al., 1998; Belsham, 2001; Danbolt, 2001). Modifications in glutamatergic transmission can have toxic effects for the central nervous system of mammals. Accordingly, overstimulation of glutamate receptors, mainly of the NMDA (*N*-methyl-D-aspartate) subtype, is associated with a variety of acute and degenerative neuropathological conditions, including ischemia, Alzheimer's disease, and amyotrophic lateral sclerosis (Lipton and Rosenberg, 1994). Furthermore, glutamatergic dysfunction is now accepted as an important factor in the etiology of schizophrenia and major depression (Tsai et al., 1995; Carlsson et al., 1999; Berk et al., 1995, 2001; Belsham, 2001). Therefore, the sensitivity of platelets to glutamate is increased in patients with major depression and schizophrenia, but it was not modified in bipolar patients (Berk et al., 2000). Recently, changes in the components of central glutamatergic transmission have been implicated in other psychiatric illnesses including mood disorders (McCullumsmith and Meador-Woodruff, 2002).

Platelets express glutamate receptors that have an anti-aggregating role and glutamate transporters that are analogous to those found in the brain (Franconi et al., 1996, 1998; Ferrarese et al., 2000, 2001a,b). Of particular importance is that high affinity glutamate transport is impaired in a variety of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, parkinsonism and epileptic patients (Ferrarese et al., 2000, 2001a,b; Rainesalo et al., 2003). Taken together, these results suggest that peripheral glutamate transport by platelets can be changed in diseases that are associated with changes in glutamatergic neurotransmission. The involvement of glutamate in the etiology of bipolar disorders has been advanced indirectly through in vitro and animal studies (Dixon and Hokin, 1998). Glutamate transport in isolated nerve endings from mouse brain is modified by chronic lithium treatment, and the response of cultured neurons to glutamate agonists is reduced after chronic exposure to lithium (Dixon and Hokin, 1998). However, studies dealing with peripheral changes in glutamate transport in bipolar mood disorders are lacking in the literature. Therefore, the objective of this study was to determine high affinity glutamate uptake by platelets from bipolar I disorder patients with manic episodes or under lithium treatment.

2. Methods

2.1. Patients

Fifteen patients with bipolar I disorder were included in this study. They were all patients of the 'Hospital Universitario' from the Universidade Federal de Santa Maria (HUSM), Brazil. The protocol study was reviewed and approved by the appropriate institutional review board from Hospital Universitario (CCS, UFSM, protocol number 8081) in accordance with the standards and guidelines established in the current amendment of the Declaration of Helsinki, and consistent with good clinical practice and applicable regulatory requirements. Written informed consent was obtained from all patients before any study-related activities.

The experimental study included seven patients who were under lithium treatment (600–1800 mg/day for at least 6 months) and were classified as stabilized patients by the DMS-IV (the plasma lithium levels of these patients range from 0.6 to 1.2 mmol/l; mean ± SD was 0.92 ± 0.13, $n = 7$). These patients visited regularly the psychiatric outpatient clinic for mood disorders at HUSM (at least one visit a month) and did not receive other drugs for treating mood disorders. Eight patients, classified as in mania by DMS-IV, were not receiving any medication. The drug-free patients were included in the study after familial approval. They were randomly selected from patients attending the psychiatry emergency service at University Hospital of Santa Maria (HUSM). The demographic data from patients and controls are presented in Table 1. The manic episode was not necessarily the first episode of these patients; however, they had not received medication for more than 1 month. Furthermore, six of these eight patients showed psychotic symptoms. Inclusion/exclusion criteria for patients were based on DSM-IV, the control subjects should not be using any psychoactive

Table 1
Demographic characterization of the sample

Group	*N*	Male	Female	Age (min–max)
Control	14	6	8	38.3 ± 10.0 (18–57)
Bipolar-I under Li^+ treatment	7	3	4	40.2 ± 14.0 (23–62)
Bipolar-I under manic episode	8	3	5	34.9 ± 14.1 (18–57)